
بسم الله الرحمن الرحيم
In The Name Of ALLAH
The Most Gracious, The Most Merciful

Armed Forces College of Medicine

AFCM

Corticosteroids Preparations 2

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture you will be able to:

1)Explain the adverse effects of glucocorticoids

2)Explain the precautions & contraindications to glucocorticoids

3)Identify the mineralocorticoids & ACTH preparations

4)Discuss the role of Inhibitors of adrenocorticoid biosynthesis

Adverse effects

DO NOT→ sudden STOP after long use

→ Acute Addisonian Crisis.

1) Iatrogenic **Cushing's disease**.

Moon face, Buffalo hump & muscle weakness.

2) **Osteoporosis** : most common

- suppress intestinal Ca^{2+} absorption.

(Anti-vitamin D → Hypocalcemia)

- Catabolic effect on bone.

(↑ Osteoclst & ↓ Osteoblast activities)

3) Hypertension & edema .

4) Hyperglycemia may develop and lead to diabetes mellitus.

5) Hypokalemia → Worsens Digitalis toxicity.

6) ↑ Peptic ulcer .

7) Cataract & ↑ Intra-ocular pressure → Glaucoma.
with long-term corticosteroid therapy.

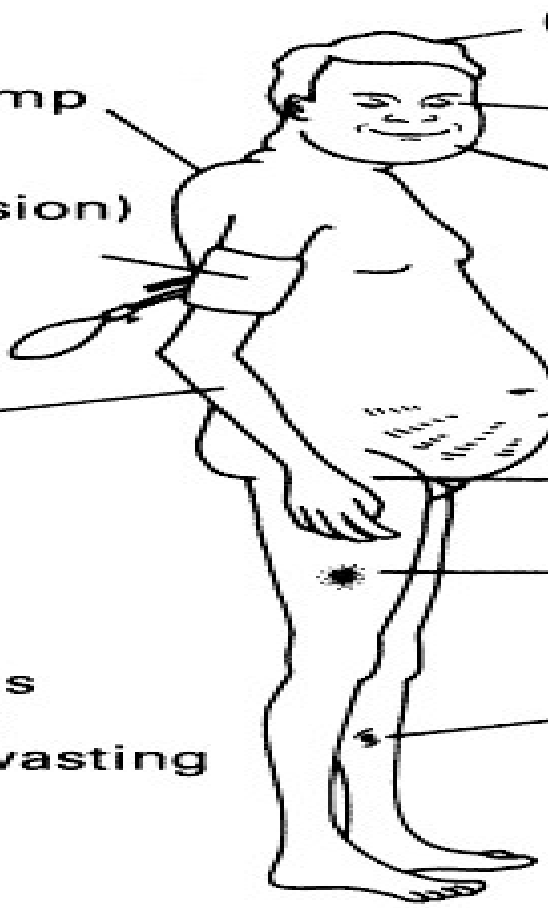
8) Sublaxation of joints on repeated intra-articular inj.

9) Immunosuppressant → ↑ Susceptibility to infection, flare up present infection (T.B. lesion).

10) Psychological disturbances.

11) Teratogenicity.

Euphoria
(though sometimes depression or psychotic symptoms, and emotional lability)



(Benign intracranial hypertension)
Buffalo hump
(Cataracts)
Moon face, with red (plethoric) cheeks
(Hypertension)
Increased abdominal fat
Thinning of skin
(Avascular necrosis of femoral head)
Easy bruising
Thin arms and legs: muscle wasting
Poor wound healing

Also:

Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
Increased susceptibility to infection
Obesity

Precautions During Long Term Gluco.Therapy

1- **Gradual withdrawal.**

2-Test for glucose in urine

3- Routine X-ray spine.

4- Add anabolics.

5- Weight estimation.

6- Measure blood pressure.

7- Avoid in Digitalis toxicity.

8- Increase dose in **stress.**

9- Diet should by ***Rich*** in Proteins, K^{+} & Ca^{2+} & ***Low*** in NaCl.

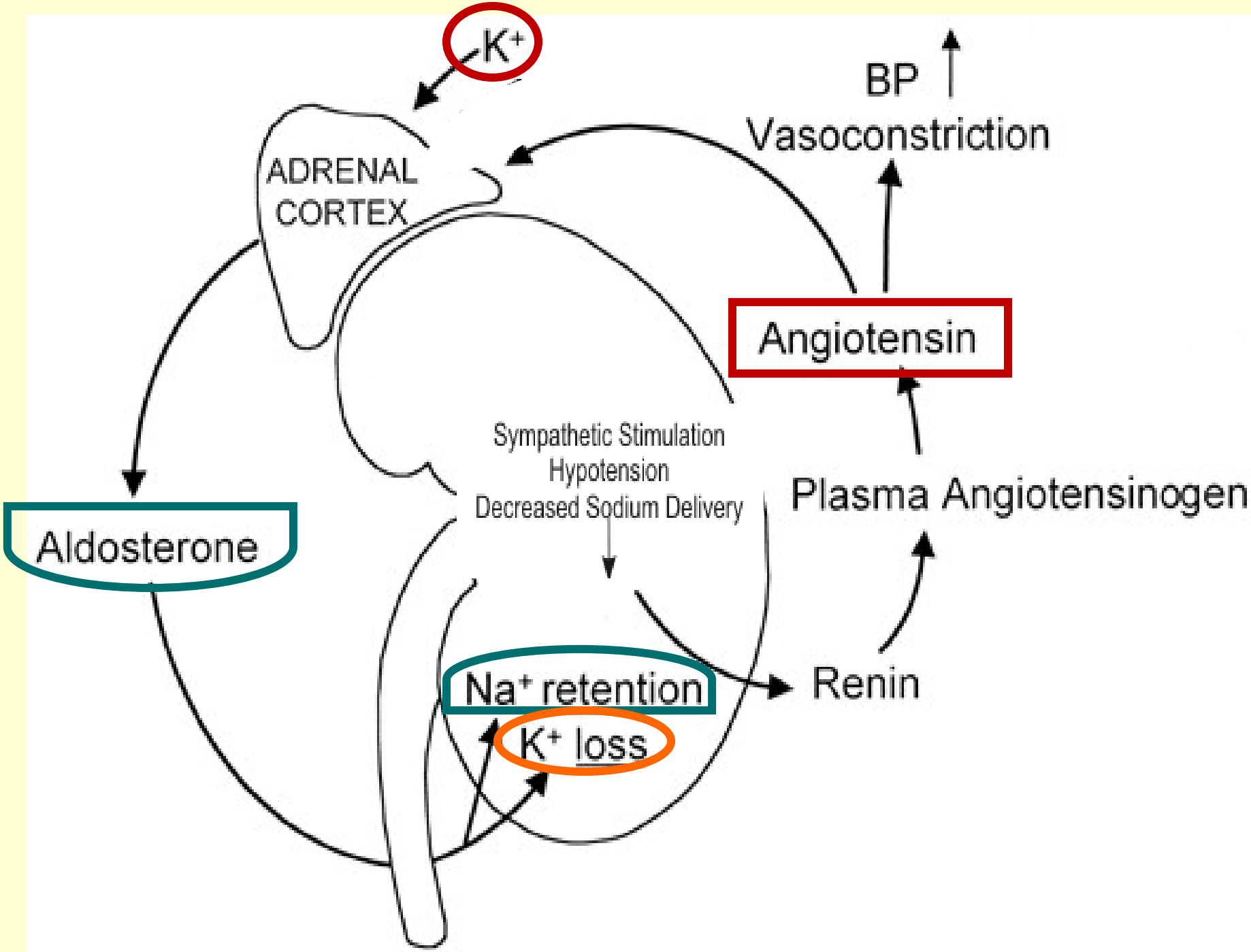
Contraindications

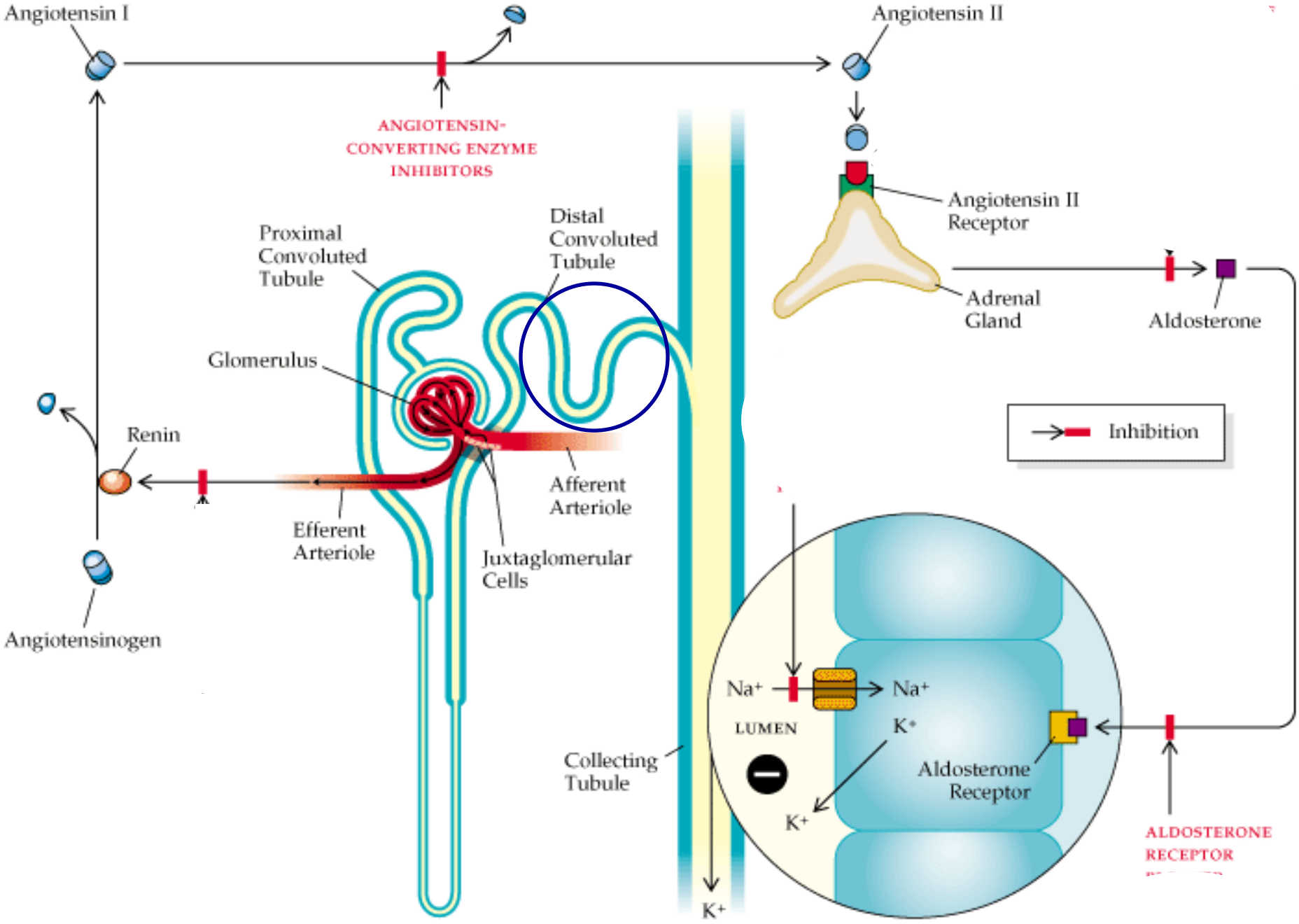
- Abrupt withdrawal
- Osteoporosis
- Hypertension & heart failure
- Diabetes mellitus
- Peptic ulcer
- Glaucoma
- Infection :specially viral & T.B
- Psychosis
- Thromboembolic diseases
- During pregnancy
- Cushing’s disease

Mineralocorticoids

1) Aldosterone
2) Des-Oxy-Corticosterone
3) Fludrocortisone Acetate

Aldosterone


K+
BP
Vasoconstriction
ADRENAL
CORTEX
Angiotensin
Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery
Plasma Angiotensinogen
Aldosterone
Na+ retention
K+ loss
Renin


Angiotensin I
ANGIOTENSIN-
CONVERTING ENZYME
INHIBITORS
Angiotensin II
Angiotensin II
Receptor
Adrenal
Gland
Aldosterone
Proximal
Convoluted
Tubule
Distal
Convoluted
Tubule
Glomerulus
Renin
Afferent
Arteriole
Efferent
Arteriole
Juxtaglomerular
Cells
Angiotensinogen
Inhibition
Collecting
Tubule
Na+
Na+
LUMEN
K+
K+
Aldosterone
Receptor
ALDOSTERONE
RECEPTOR

Causes of Hyper-Aldosteronism:

1- Primary → Adenoma in Zona glomerulosa

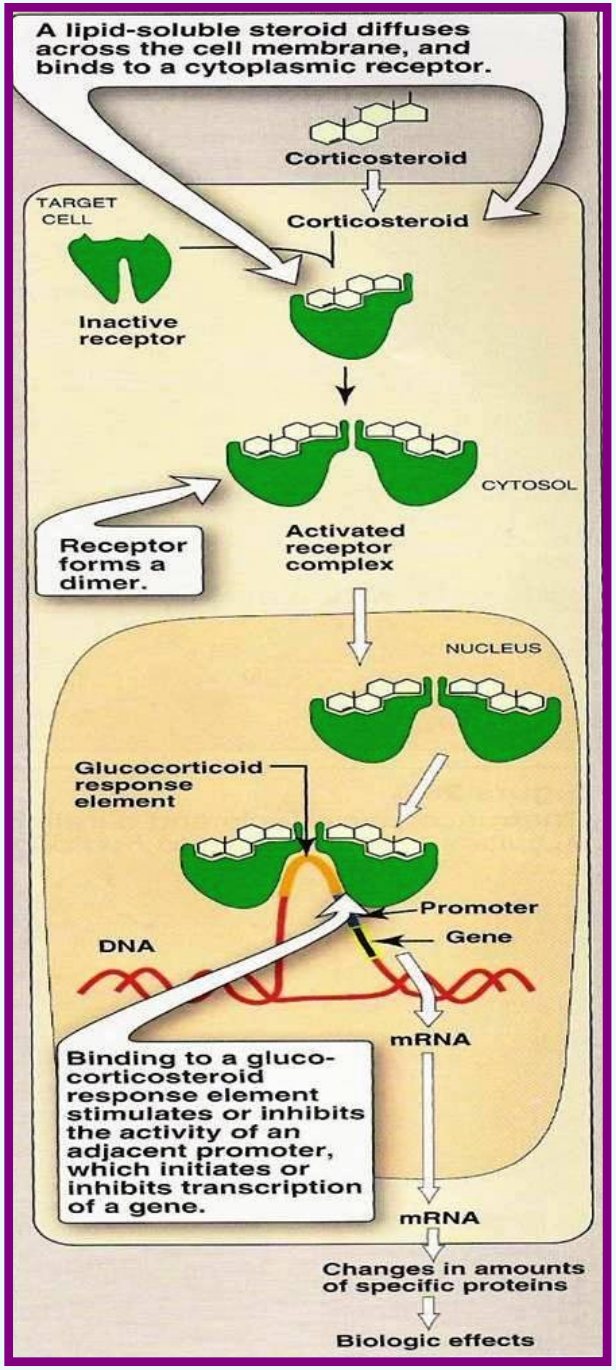
→ Conn's disease.

2- Secondary to:

Heart failure, Nephrotic syndrome & Liver disease

Spironolactone (***Aldosterone*** antagonist) is useful as K^+-Retaining diuretic especially in cases of Hyper-aldosteronism

Mechanism of action of mineralocorticoids



Genomic effects ⇒ **Most of actions mineralocorticoids** bind to specific intracellular cytoplasmic receptors in target tissues.

- Receptor-Hormone complex translocates into the nucleus.
- Gene expression → DNA transcription → mRNA → Protein synthesis → Na^+-channels & Na^+/K^+ ATPase.
- ***Non-Genomic effect*** Aldosterone → ↑ Memb. receptors →↑ Na^+/K^+ Exchang.

Des-Oxy-Corticosterone (D.O.C.)

1- ***Pure mineralocorticoid*** with ***NO*** glucocorticoids activity.

2- 1/100 activity of aldosterone.

3- **Used to *replace* mineralocorticoid activity *in Addison's disease.***

4- **NOT effective orally** due to **extensive hepatic first pass** metabolism **so it is administered by**:

- Sublingual,
- I.M
- Subcutaneous Pellet Implantation (/ 6 months).

Fludrocortisone Acetate

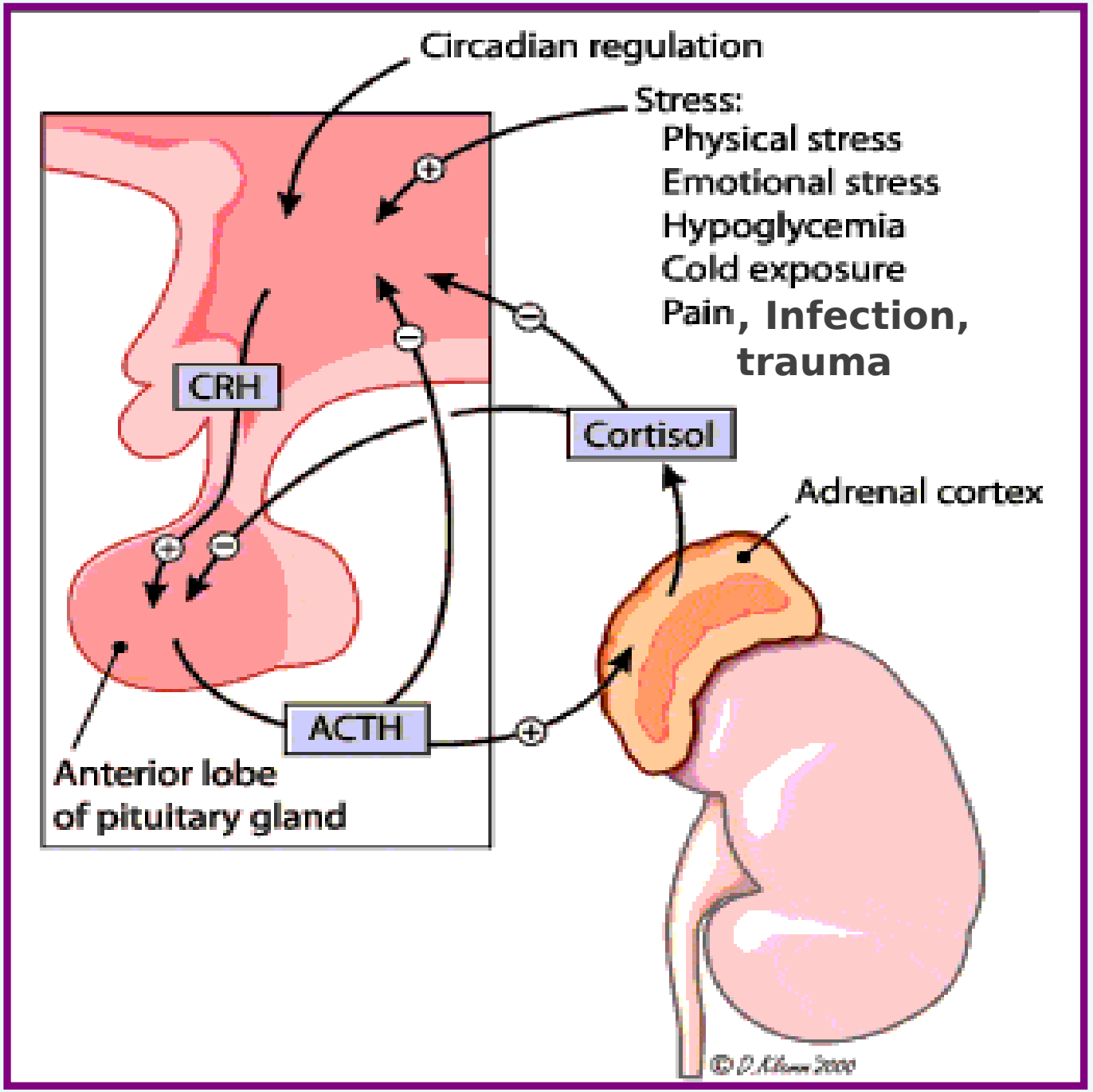
1- **Synthetic mineralocorticoid**.

2- **Mineralocorticoid & Glucocorticoid activities**.

3- Useful **orally** to **replace mineralocorticoid activity in Addison's disease.**

Des-Oxy-Corticosterone (D.O.C.)	**Fludrocortisone Acetate**
Pure mineralocorticoid	**Mineralocorticoid & Glucocorticoid**
NOT effective Orally SL, I.M & SC Pellet Implantation	Useful **orally**
replace* mineralocorticoid *in Addison's disease.	

Adreno-Cortico-Trophic-Hormone (A.C.T.H.)


Circadian regulation
Stress:
Physical stress
Emotional stress
Hypoglycemia
Cold exposure
Pain, Infection, trauma
CRH
Cortisol
Adrenal cortex
ACTH
Anterior lobe of pituitary gland

Preparations

1) **Corticotrophin** (A.C.T.H.)

2) **Synthetic Tetracosactrin**
"Synacthen" → First 24 amino acids of A.C.T.H. → Same effect of A.C.T.H. & **less antigenic**.

Therapeutic Uses of A.C.T.H

↑ Synthesis & Release of Cortisol

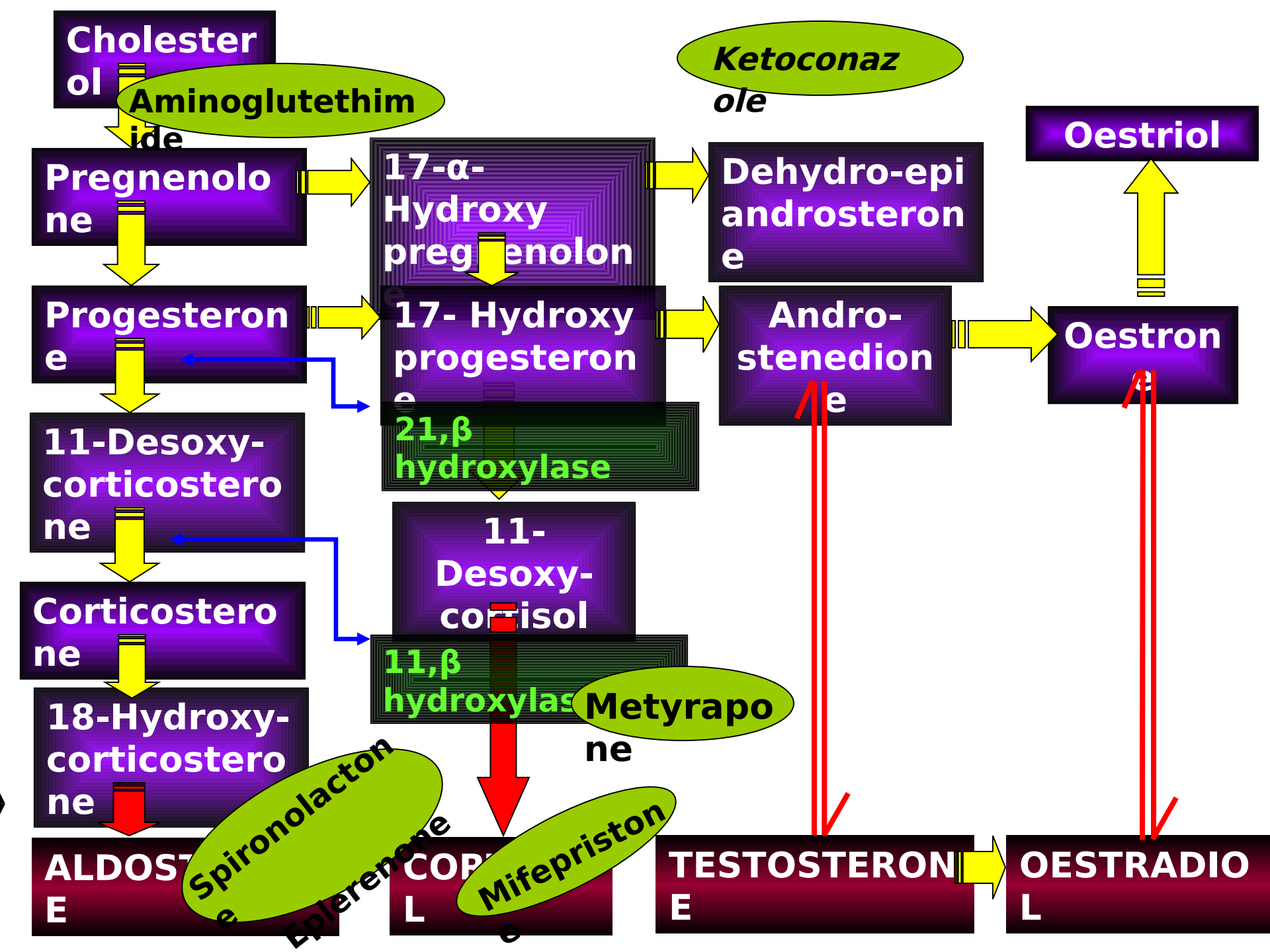
1)Same indications of Cortisol

Except **primary Addison's disease**

2) Help withdrawal of steroid therapy after long use.

3)Test the function of adrenal cortex → Estimate plasma cortisol.

Inhibitors Of Adrenocorticoid Biosynthesis


Cholesterol
Aminoglutethimide
Ketoconazole
Pregnenolone
17-α-Hydroxy pregnenolon
Dehydro-epi androsterone
Oestriol
Progesterone
17- Hydroxy progesterone
Andro-stenedione
Oestrone
21,β hydroxylase
11-Desoxy-corticosterone
11-Desoxy-cortisol
11,β hydroxylas
Metyrapone
Corticosterone
18-Hydroxy-corticosterone
Spironolactone
Eplerenone
Mifepriston
ALDOSTE
CORL
TESTOSTERONE
OESTRADIOL

1) Aminoglutethimide:

- Inhibiting the conversion of :

  Cholesterol to ------ pregnenolone.
- Reduced synthesis of all hormonally active steroids.
- Useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids
- Used in the treatment of breast cancer to reduce or eliminate androgen and estrogen production. [*Tamoxifen* has largely replaced it]

2) ***Ketoconazole:***

- Antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis.
- used in the treatment of patients with Cushing syndrome.

3) Metyrapone:

- blocking the final step (11-hydroxylation) in glucocorticoid synthesis,
- used for the treatment of pregnant women with Cushing syndrome.
- ↑11-deoxycortisol, 11-deoxycorticosterone.

  and adrenal androgens.

4) Mifepristone:

- At high doses, *mifepristone* is a potent glucocorticoid antagonist as well as an antiprogestin.
- limited to treatment of inoperable patients with ectopic ACTH syndrome.

5) Spironolactone:

- Aldosterone Antagonist ---- effective against hyperaldosteronism.

- In the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle.
- **Adverse effects :** hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

6) Eplerenone:

- An aldosterone antagonist (antihypertensive drug)
- avoids the unwanted side effects of *spironlactone*

Corticosteroids are usually indicated in all the following conditions EXCEPT:

1. Osteoarthritic inflammation
2. Diagnosis of Cushing’s syndrome
3. Herpes simplex of the eye
4. Addison’s disease
5. severe acute bronchial asthma

The following arrangement of different corticosteroids is correct as regarding increasing anti-inflammatory activity:

1. Cortisol – Prednisone – Dexamethazone -Aldosterone
2. Prednisone – Aldosterone – Dexamethazone - Cortisol
3. Aldosterone - Prednisone – Cortisol – Dexamethazone
4. Aldosterone - Cortisol – Prednisone - Dexamethazone

Prolonged therapy with glucocorticoids can produce all of the following adverse effects **EXCEPT:**

1. Peptic ulcer
2. Increased susceptibility to infection
3. Myopathy and osteoporosis
4. Hypoglycemia
5. Suppression of pituitary-adrenal function

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.


THANK
YOU

Congenital Adrenal Hyperplasia

- This condition is also known as **Adrenogenital syndrome**
- A Family of autosomal recessive disorders of steroid hormone production in the adrenal glands leading to a **deficiency of cortisol**
- **Genetically induced enzyme deficiencies** in the pathways that produce steroid hormones. Deficiency of the enzyme **21-hydroxylase accounts for 95%** of affected patients.
- The pituitary, sensing the deficiency, secretes massive amounts of the stimulating hormone **corticotropin** to bring the cortisol levels up to normal. This hormone in turn causes the adrenal glands to overproduce certain intermediary hormones which have testosterone-like effects on the fetus and child, leading to so-called **"virilization.“**
- **Virilized children grow abnormally rapidly** because of accelerated bone maturation and go through puberty very early but ultimately wind up being quite short as adults.
- About **75% of affected infants have the "salt-losing" form** of the disorder, in which the salt-retaining steroid hormone is deficient . This is **potentially fatal if undiagnosed.**
- Treatment involves **hormone replacement.** Treatment is monitored by measures of blood electrolytes, by suppression of overly-rapid sexual maturation, and by monitoring of the skeletal maturation rate